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In This Issue

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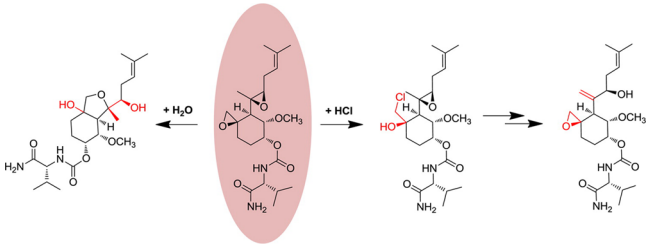
BASIS FOR THE ACTIVITY OF FUMAGILLIN ANALOGUES IN THE GASTRIC ENVIRONMENT

Fumagillin is an antiangiogenic agent, the analogues of which have entered the clinic for cancer therapy. These compounds target the enzyme methionine aminopeptidase-2 (MetAP2) via reactive spiroepoxide functionality. Recently, a fumagillin analogue, PPI-2458, with improved safety and pharmacokinetic properties was reported. Although this compound is prone to chemical degradation in vivo, PPI-2458 retained its potency when administered orally. In the current issue, Arico-Muendel et al. (DOI: 10.1021/ml3003633) seek to better understand the properties of this promising compound.

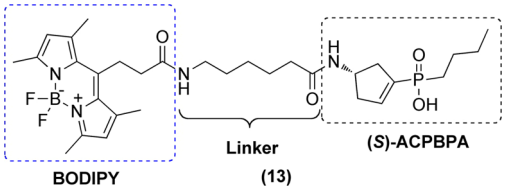
In an acidic environment that simulated the environment in the stomach, PPI-2458 degraded into four major compounds, two of which retained MetAP2 inhibitory activity. The two inhibitory compounds were found to be chlorohydrins, which likely reversed back to an active spiroepoxide upon passage into a neutral pH environment, such as the gut or bloodstream. This study demonstrated a new mechanism by which reactive compounds can survive the harsh gastric environment and retain potency.



TOOL FOR VISUALIZING GABA$_C$ RECEPTORS

γ-Aminobutyric acid (GABA) is the most common inhibitory neurotransmitter found in the central nervous system that plays a role in regulating neuronal excitation. GABA elicits its effects by binding GABA$_A$, GABA$_B$, and GABA$_C$ receptors. GABA$_c$ receptors, which are composed of five ρ subunits, are therapeutic targets for treating myopia, sleep disorders, and memory disorders. In spite of the importance of this receptor to drug development, little information is available regarding the downstream processes triggered by ligand binding to GABA$_c$ receptors. To bridge this gap, Gavande et al. (DOI: 10.1021/ml300476v) provide novel tools for studying the localization and function of GABA$_C$ receptors.

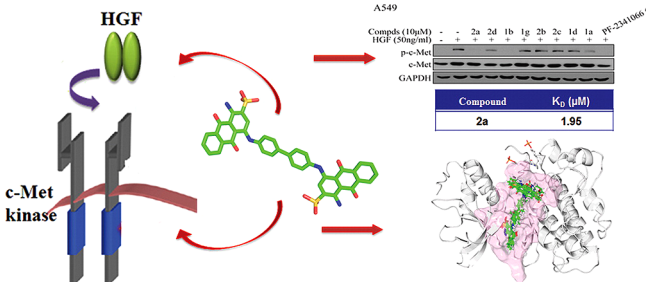
In mammals, GABA$_C$ receptors comprise a pentameric combination of ρ_1, ρ_2, and ρ_3 subunits. The authors developed a variety of fluorescent ligands conjugated to GABA$_C$ antagonist, (*S*)-4-ACPBPA, to offer a selective and potent agent, (S)-4-ACPBPA-C5-BODIPY, for visualizing ρ_1 GABA$_C$ receptors in vivo. This new agent provides a significant breakthrough for studying the pathophysiological processes dependent on GABA$_C$ receptor function.



NEW LEAD COMPOUNDS FOR CANCER THERAPY

c-Met kinase is a membrane receptor protein and a product of the *MET* proto-oncogene for which Hepatocyte Growth Factor (HGF) is the only known ligand. This tyrosine kinase receptor plays a vital role in cell survival and embryonic development. Modulation of this kinase pathway has emerged as an approach to cancer therapy. In the current issue, Liang et al. (DOI: 10.1021/ml4000047) offers a class of new inhibitors of the c-Met kinase signaling pathway.

Combination of computational and experimental approaches showed that anthraquinone derivatives are potent c-Met kinase inhibitors. Anthraquinone derivatives specifically suppress the extracellular HGF-dependent pathway. Subsequent work demonstrated that the most potent derivative also targeted HGF with a high binding affinity (K_D = 1.95 μM). These dual-acting compounds provide a new rationale for designing c-Met kinase signaling pathway inhibitors.



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